

REMARKS

Status of the claims

Claims 7 and 9-22 are pending and stand rejected. Claims 7, 9-14 and 16-17 are amended. Claims 1-6, 8 and 23-54 were canceled previously. Claims 19-22 are canceled herein. No new matter is added.

Claim amendments

Claim 7 was amended to incorporate the limitation of gravity release of claims 12 and 13. Additionally, claim 7 was amended to recite "dispensers comprising a pipette tip" and to delete "small" from the claim. Claims 12 and 13 were amended to recite "causing said droplet to release through gravity" to properly depend from amended claim 7. Claims 9-14 and 16-17 were amended to delete "pipette-based".

Rejections Under 35 USC §112, second paragraph

Claims 7 and 9-22 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

The Examiner states it is not clear within the claimed context in what respect the dispenser is based or like a pipette. Applicants have amended claim 7 to recite "dispensers comprising pipette tips" and have deleted the phrase "pipette-based" from claims 9-14 and 16-17. The Examiner states that the term "small" in claim 7 is a relative term which renders the claim indefinite. Applicants have deleted "small" from the claims. The Examiner states that claims 19-22 do not further limit the claimed method of forming a miniarray in that they are drawn to a method of using. Applicants have canceled claims 19-22. Accordingly, in view of the claim amendments presented herein, Applicant respectfully requests that the rejection of claims 7 and 9-18 under 35 USC §112, second paragraph, be withdrawn.

Rejections Under 35 USC §103(a)

Claims 7 and 9-10 and 12-22 are rejected under 35 USC §103(a) as being unpatentable over *Brown et al.* (U.S. Patent 5,807,522) or *Van Ness et al.* (U.S. Patent

6,248,521) in view of *Chee et al.* (U.S. Patent No. 6,429,027) or *Tisonne et al.* (U.S. Patent No. 6,063,339). This rejection is traversed.

The Examiner states that *Brown et al.* discloses at col. 3, line 23 up to col. 4, line 59 a method of forming a microarray of analyte-assay regions on a solid support, where each region in the array has a known amount of a selected, analyte-specific reagent. The method comprises loading a solution of a selected analyte-specific reagent in a reagent-dispensing device having an elongate capillary channel (pipette-based dispensers as claimed) (i) formed by spaced-apart, coextensive elongate members, (ii) adapted to hold a quantity of the reagent solution and (iii) having a tip region at which aqueous solution in the channel forms a meniscus. The tip of the dispensing device is tapped against a solid support at a defined position on the support surface with an impulse effective to break the meniscus in the capillary channel, and deposit a selected volume of solution on the surface. The two steps are repeated until the desired array is formed. See further col. 6, line 64 up to col. 9, line 50 and the claims.

The Examiner states that *Van Ness et al.* is discussed in the last Office action and below. The Examiner stated in the last Office Action that *Van Ness et al.* discloses basically the same or similar method to *Brown et al.* The Examiner also stated that *Van Ness et al.* disclose a CTC spots of 25-500 microns. The Examiner quotes *Van Ness et al.* in that "... a variety of printing methods are available for applying...to a solid substrate in an array pattern. As a general guideline, the delivery mechanism must be capable of position very small amounts of liquids...in small regions...where the regions are very close to one another, e.g. 25-500 microns center to center."

The Examiner states that neither *Brown et al.* nor *Van Ness et al.* disclose a miniarray as claimed. However, the Examiner states that *Chee et al.* disclose at col. 6, lines 1-43 array compositions can be made into a high density, moderate density, low or very low density array. *Chee* discloses that the size of the array will depend on the composition and end use of the array. Low density arrays are generally less than 10,000, with from about 1,000 to about 5,000 cm being preferred. Very low density arrays are less than 1,000, with from about 10 to about 1000 being preferred, and from about 100 to about 500 cm being particularly preferred. In addition, one advantage of the present compositions is that particularly through the use of fiber optic technology.

The Examiner states that **Tisone** discloses at col. 25, lines 19-22 that a dispenser can be programmed so as to transform one or more well plate arrays into a new or different high or low density array. For example, a series of two dimensional arrays may be transformed into rows or columns of a larger high-density array, or arrays may be transposed or inverted. Direct 1:1 mapping can also be achieved by operating the dispense heads in parallel synchronous line mode to produce 8 drops on each slide with a spacing of 9 mm. Other modes and variations for the use and operation of the invention will be apparent to those skilled in the art.

Thus, the Examiner states it would have been obvious to one having ordinary skill in the art at the time the invention was made to make a miniarray (i.e., low density array) using the method of **Brown et al.**, as taught by either **Chee** or **Tisone**. Each of **Chee** or **Tisone** positively teaches that either a high density (microarray) or a low density miniarray can be made. That such arrays are useful in fiber optic technology would motivate one in skill in the art to use either a high or low density array as taught by e.g., **Chee**.

Brown et al. teach a method for forming microarrays of biological samples on a support by dispensing a known volume of a reagent at each selected array position by tapping a capillary dispenser on the support under conditions effective to draw a defined volume of liquid onto the support (Abstract). The capillary dispenser has an elongate capillary channel with a tip. The capillary dispenser is loaded by dipping the tip into the solution which loads via capillary action. The aqueous solution in the channel forms a meniscus. The tip is tapped against a solid support with an impulse effective to break the meniscus in the capillary channel to deposit the liquid in a flowing manner (col. 3, ll. 23-50; col. 7, ll. 55 to col. 8, ll. 9).

Brown et al. define a microarray as having, inter alia, typical dimensions in the range of between about 10-250 microns and are separated from other regions in the array by about the same distance (col. 6, ll. 32-37). In col. 9, ll. 35-39, **Brown et al.** state that, as they indicated above, i.e., in Table 1, the diameter of each region is preferably between about 20-200 microns, which falls within the defined range, however the center to center spacing, which **Brown et al.** define as about the same as the diameter, is in the range of 20-400 microns.

Van Ness *et al.* teach a method of for performing amplification and other enzymatic reactions on nucleic acid molecules that have been printed onto a solid substrate, such as a silicon wafer or glass slide (Abstract). Van Ness *et al.* generally teach that the delivery mechanism need only meet the requirements quoted by the Examiner and states such delivery mechanism may employ an automated system such as ink jet printing using multiple heads or very fine pipettes. Preferably a preferred means of printing uses spring probes (col. 6, ll. 54 to col. 7, ll. 29). Van Ness *et al.* teach that CTC may be 25 to 500 microns.

Chee *et al.* teach methods and compositions for decoding microsphere array sensors (Abstract). Chee *et al.* produce an array of arrays in a microtiter plate where each individual well comprises an array (col. 4, ll. 19-31). Chee *et al.* teach that a composite array is a plurality of individual arrays (col. 6, ll. 44-46) and each individual array may comprise from 2 to a billion bioactive agents on equal numbers of microbead substrates to range from very high density to very low density (col. 6, ll. 1-27).

Tissone *et al.* teach a dispensing apparatus and method to accurately and precisely dispensing various desired patterns of reagent onto a substrate or other receptive surface or receptacle. The dispensing apparatus comprises one to eight dispensing heads having an inlet end and an outlet end which are responsive to a signal to provide for relative X, X-Y or X-Y-Z motion between the substrate and the dispensing head (Abstract; col. 4, ll. 14-37).

Applicants invention is discussed *supra*. Applicants have canceled claims 19-22. As amended, independent claim 7 recites a method of forming a miniarray that, inter alia, requires (1) aspirating the solution into the pipette tip comprising the dispenser; (2) applying pressure to the solution to form a defined drop at the end of the pipette tip; (3) and touching the defined drop to the substrate and causing the droplet to release through the action of gravity. Neither Brown *et al.* nor Van Ness *et al.* teach these claim elements. Van Ness *et al.* teach that sample pick-up, transfer and micro-droplet deposition is greatly enhanced when using a liquid transfer device that has a hydrophilic surface, particularly when that device is a modified spring probe that is soaked in a hydrophilic substance to improve the flow of the solution into or out of the of the dispenser (col. 6, ll. 66 to col. 7, ll. 29). Particularly, in Brown *et al.* the inventive concept is to use a capillary dispenser

which is loaded and unloaded via capillary action. The meniscus formed at the end of the capillary is caused to flow onto the substrate by tapping the end of the capillary against the substrate to release the surface tension holding the meniscus so that the solution can be withdrawn via the capillary action from the dispenser.

Applicant submits that a capillary is a distinct means of dispensing from a pipette and specifically relies on capillary action to load and dispense fluids. Applicant's invention requires a pipette tip which is designed to aspirate fluids into and deliver fluids both under pressure. The shape of the tip is designed such that pressure applied to the solution in the tip will form a defined drop at the tip which requires the action of gravity to release the drop. A capillary tube is not designed to perform these actions.

No suggestion or teaching is found in either *Brown et al.* or *Van Ness et al.* to modify the method of dispensing to use a dispenser comprising pipette tips. One of ordinary skill in the art would not be motivated to do so because the capillary dispenser and tapping action disclosed in *Brown et al.* is designed specifically to controllably dispense spots of defined volume measured in nanoliters, diameter within a range of about 10-250 microns and CTC within a range of about 10-400 microns to form a microarray. Additionally, one of ordinary skill in the art would not be motivated to modify *Van Ness et al.* because the inventive concept is drawn to methods of amplification and other enzymatic reactions performed on nucleic acid arrays using standard array forming techniques. No motivation is found to modify the formation of the array because *Van Ness et al.* state that standard techniques using spring probes, for example, are sufficient as long as the spots dispensed have a small enough volume and a CTC within the range of about 25-500 microns which is similar to the CTC in the microarray of *Brown et al.*

Combining *Chee et al.* or *Tisone et al.* with *Brown et al.* or *Van Ness et al.* does not remedy these deficiencies. Neither *Chee et al.* nor *Tisone et al.* provide a teaching or suggestion to modify *Brown et al.* or *Van Ness et al.* to dispense the solution to form as recited in amended claim 7 to form Applicant's miniarray. Therefore, the disclosure of the ranges of the CTC in the arrays formed or whether the array is high- or low-density is moot.

Furthermore, claims 9-10 and 12-18 depend directly from amended claim 7 and further limit the dispensers and the substrate. As the combination of *Brown et al.* or

Van Ness et al. with *Chee et al.* and *Tisone et al.* cannot render amended claim 7 obvious, then neither are dependent claims 9-10 and 12-18 rendered obvious. Accordingly, in view of the amendments and arguments presented herein, Applicant respectfully requests that the rejection of claims 7, 9-10 and 12-18 under 35 U.S.C. §103(a) be withdrawn.

Claims 11 is rejected under 35 USC §103(a) as being unpatentable over *Brown et al.* in view of either *Chee et al.* or *Tisonne et al.*, as applied to claims 7 and 9-10 and 12-22 above, and further in view of *Lange* (abstract). This rejection is respectfully traversed.

The Examiner states that *Brown et al.* does not disclose a disposable tips dispensers. The Examiner states that *Lange* discloses the use of a disposable pipette. It would have been obvious to one of ordinary skill in the art to use a disposable unit in the method of *Brown* as taught by *Lange* because a disposable dispenser unit would obviously produce a contamination free device for pipetting.


Brown et al. is as discussed by Applicant *supra*. Applicant's invention is as discussed *supra*. *Lange* teaches a contamination free device for pipetting liquids with a reusable dispensing element and a disposable double tip. Applicant maintains that the combination of *Brown et al.* with *Chee et al.* or *Tisonne et al.* does not render claims 7, 9-10 and 12-18 obvious for the reasons discussed. As one of ordinary skill in the art would not be motivated to modify the capillary dispenser in *Brown et al.* with a pipette and as the combination of either *Chee et al.* or *Tisone et al.* with *Brown et al.* does not remedy this deficiency, the inclusion of the disposable pipette of *Lange* in the combination also does not remedy this deficiency. Therefore, particularly in view that claim 11 depends from amended claim 7, the combination of *Brown et al.* with *Chee et al.* or *Tisone et al.* and *Lange et al.* cannot render dependent claim 11 obvious. Accordingly, in view of the amendments and arguments presented, Applicant requests that the rejection of claim 11 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed August 10, 2004. Applicant submits that claims 7 and 9-18 are in condition for allowance. If any issues remain, the Examiner is requested to telephone the undersigned attorney for immediate resolution. Applicants include a Petition for a Three Month Extension of Time.

Please credit the \$510 extension fee to the credit card identified on the enclosed Form PTO-2038. Please debit any insufficiency of fees from Deposit Account No. 07-1185 upon which the undersigned is allowed to draw.

Respectfully submitted,

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